IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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Applicant	:	Thor	
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TC/A.U.	:	1617	
Examiner	:	Yong Soo Chong	
Docket No.	:	4220-78-PUS	
Customer No.	:	22442	

Declaration of David A. Rivas, MD
37 CFR 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313

Dear Sir:

I, David A. Rivas, declare as follows:

My curriculum vitae is attached. My employment and educational history is summarized below.

Johnson & Johnson Pharmaceutical Research and Development, Senior Director, Clinical Leader [Reproductive Health/Urology] August 2004-present

GlaxoSmithKline, Director, Discovery Medicine [Urogenital], Cardiovascular & Urogenital Center for Excellence and Drug Discovery November 2003-August 2004

Pfizer, Inc., Director, Global Clinical Research [Urology] April 2003-October 2003

Pharmacia Corporation, Director, Global Clinical Research [Urology]
Associate Director, Global Clinical Research [Urology] Nov. 2000-Dec. 2002

Various Faculty Appointments, 1994-2000

Various Post Graduate Positions, 1984-1994

M.D., Jefferson Medical College of Thomas Jefferson University
Philadelphia, Pennsylvania, 1980-1984

A.B., Distinction in All Subjects, Cornell University
Ithaca, New York, 1977-1980

1. I have reviewed U.S. Patent Application 10/049,427, the Office Action dated 10/4/2005 and the references cited therein, including the McMahon et al. article cited by the Examiner in the 10/4/05 Office action (McMahon et al., J Urology, v. 161, pp. 1826-30 (1999). Treatment of Premature Ejaculation with Paroxetine Hydrochloride as Needed: 2 Single-Blind Placebo Controlled Crossover Studies).

2. McMahon et al. is a pilot study exploring the merits of paroxetine (an SSRI specifically designed to treat conditions pertaining to mood and affect and which must be administered daily to achieve and maintain the desired therapeutic effect) in the treatment of men suffering with premature ejaculation (PE). The authors study objective is 'to determine whether paroxetine as needed 3-4 hours before sexual intercourse was more efficacious than placebo in the treatment of PE.'

3. McMahon et al. does not provide sufficient information to determine whether the week 1 treatment data of Study 1 are statistically significantly different from the control data. Since McMahon et al. does not state that the week 1 treatment data of Study 1 are statistically significantly different from the control data, I would assume that they are not. Consequently, I would not rely on the week 1 data as demonstrating an increase in ejaculatory latency.

   a. In relation to Study 1, the authors state that "[t]he ejaculatory latency time for groups A and B during treatment with paroxetine as needed was statistically superior to placebo at 2, 3, and 4 weeks ($p<0.001$, table 2, fig. 1)." This statement conveys to me, as one skilled in the art, that the authors do not consider the results at week 1, shown in table 2 and figure 1, to be statistically significant. Based on the authors' characterization of this data, it would be inappropriate for one to conclude that the week 1 data in Study 1 are statistically significant.

   b. The McMahon et al. paper does not provide sufficient information (standard deviation, confidence intervals, median values and range values) to permit interpretation of the week 1 data, particularly because of the

limited sample size and because intravaginal ejaculatory latency times (IELT) tend to be variable and not normally distributed.

c. As one skilled in the art, after reviewing the McMahon et al. paper and understanding that the week 1 data in Study 1 are not statistically significant, it would be inappropriate for one to conclude that the week 1 data demonstrates a statistically significant increase over control data in ejaculatory latency time. Therefore, I would not rely on the week 1 data as demonstrating an increase in ejaculatory latency.

4. McMahon et al.'s conclusions regarding as needed dosing of paroxetine does not allow one skilled in the art to draw any conclusions about whether or not as needed use of paroxetine in the absence of priming doses is efficacious because the "as needed" use of paroxetine in McMahon et al. does not preclude priming doses.

a. As noted above, the study objective of McMahon et al. was 'to determine whether paroxetine as needed 3-4 hours before sexual intercourse was more efficacious than placebo in the treatment of premature ejaculation.'

b. McMahon et al.'s statement that initial daily treatment improves the as needed efficacy of paroxetine was based on a greater mean ejaculatory latency time in Study 2 (initial daily dosing) than in Study 1 (no initial daily dosing). (McMahon et al., p. 1829, col. 1, ll. 20-25);

c. Mean ejaculatory latency time for study Groups A-D is calculated using all data throughout the treatment phases (i.e., multiple instances of intercourse per week over 4 week treatment phases) when paroxetine had been used over a period of time;

d. Paroxetine use throughout a 4 week period, even in Study 1 without prior 2 week daily dosing, is not "in the absence of a priming dose";

e. The McMahon et al. study design did not impose a minimum time interval between intercourse episodes and therefore, paroxetine from one dose that was not cleared from the body could, in combination with a subsequent dose, result in an increase in paroxetine exposure in the patient greater than a single dose, thereby functioning as a priming dose;

f. Therefore, McMahon et al.'s statement that "paroxetine as needed is significantly better if patients are initially treated with the drug daily," which is based on mean ejaculatory latency time, is not relevant to whether paroxetine is effective in the absence of a priming dose because the "as needed" use of paroxetine in McMahon et al. was not designed to avoid a priming dose effect.

5. The present application on p. 19, ll. 20-25 describes as needed dosing in the absence of priming doses. The concept of a priming dose refers to a prior dose of a drug that has not been cleared from the body at the time of administration of a subsequent dose of the drug.

6. There are a number of scientific and methodological issues in McMahon et al. that makes one question the results and therefore, makes it difficult to draw meaningful conclusions from the study regarding the study objective or whether paroxetine can be therapeutically effective as needed in the absence of priming doses, a question that was not even contemplated by the study.

a. Primary/Secondary Premature Ejaculation. The patient characteristics in McMahon et al. (Table 1) indicate that the study included men with both primary and secondary PE. The paper, however, does not specify how the patients with primary and secondary PE were distributed between Groups A and B. It is unclear, therefore, whether an uneven distribution of primary or secondary PE patients between the Groups may have introduced some bias in the study.

b. Absence of Adverse Events. McMahon et al. state that there were no side effects reported by the patients taking paroxetine as needed in Study 1 (i.e., no headache, dizziness, somnolence, anorexia, anejaculation, gastrointestinal upset, reduced libido, erectile dysfunction, etc.). This would be unusual for any study and especially unusual for a study with a compound (paroxetine) with known side effects. This result draws into question the integrity of the data collection methods. Therefore, it is difficult to draw meaningful conclusions from the study.

c. Behavior Modification/Bias. There are two examples of potential bias in the McMahon et al. study: clinical investigator (physician) bias due to a lack of blinding of the investigator and patient bias based on stopwatch usage.

i. Blinding. Patients with PE can respond to factors other than pharmaceutical treatment, such as suggestions, even inadvertent, from a physician. The McMahon studies were single-blind studies (the patient is blinded to whether he is taking placebo or drug, but the clinician is not). Therefore, the physicians could have provided inadvertent suggestions to patients that they would or would not see an effect based on whether paroxetine or placebo was being administered, thereby influencing the reported results to show a stronger treatment effect. The McMahon et al. study, being a single blind, rather than a double blind study, calls the results of the study into question, making it difficult to make meaningful conclusions.

ii. Stopwatch Measurement. McMahon et al. did not report the directions for stopwatch measurement of ejaculatory latency time. The manner in which this time interval is measured (e.g., whether the stopwatch is held by the patient or his partner) can introduce bias into reported results, particularly in a single blind study. This factor also raises questions about the reported results making meaningful conclusions based on the study difficult to draw.

d. Pretreatment Values. McMahon et al. report pretreatment values of IELT based on a three week baseline period whereas the pretreatment values of coitus frequency were based on a three month pretreatment period, and the study measures of IELT and coitus frequency are based on one week values. These differences in measurements make meaningful conclusions based on the results difficult.

7. I hereby declare that all statements made herein of my own are true and that all statements made on information and belief are believed to be true; and

further that the statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the subject application or any patent issuing therefrom.

21 July 2006

Date

David A. Rivas, MD